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3

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WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES, AND  
TOXIC SUBSTANCES

TXR No.: 0053465

**MEMORANDUM**

DATE: June 13, 2005

SUBJECT: **THIAMETHOXAM:** Report of the Cancer Assessment Review Committee  
PC Code: 060109

FROM: Jessica Kidwell, Executive Secretary *Jessica Kidwell*  
Cancer Assessment Review Committee  
Health Effects Division (7509C)

TO: Alan Levy, Toxicologist (RAB2)  
Mike Doherty, Risk Assessor (RAB2)  
Health Effects Division (7509C)

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Insecticide/Rodenticide Branch, Registration Division (7505C)

The Cancer Assessment Review Committee met on April 27, 2005 to evaluate the carcinogenic potential of Thiamethoxam. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher  
Y. Woo

*CANCER ASSESSMENT DOCUMENT*

EVALUATION OF THE CARCINOGENIC POTENTIAL OF  
***THIAMETHOXAM***

PC Code 060109

FINAL  
June 13, 2005

**CANCER ASSESSMENT REVIEW COMMITTEE**  
**HEALTH EFFECTS DIVISION**  
**OFFICE OF PESTICIDE PROGRAMS**

THIAMETHOXAM

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DATA PRESENTATION:

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Alan Levy, Toxicologist.

DOCUMENT PREPARATION:

Jessica Kidwell  
Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE:

(Signature indicates concurrence with the assessment unless otherwise stated).

Karl Baetcke

Karl Baetcke

Lori Brunzman, Statistician

Jess Rowland for Lori Brunzman

William Burnam, Chair

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Nancy McCarroll

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Tim McMahon

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Jess Rowland

Jess Rowland

Linda Taylor

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NON-COMMITTEE MEMBERS IN ATTENDANCE

(Signature indicates concurrence with the pathology report)

Doug Wolf, Pathologist, EPA/ORD/NHEERL  
(conference call)

See attached sheet

OTHER ATTENDEES: Kelly Schumacher (HED/RAB2), Karlyn Bailey (HED/RAB2),  
Christina Swartz (HED/RAB2)

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## DATA PRESENTATION:

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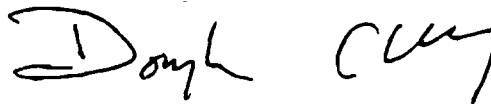
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Doug Wolf, Pathologist, EPA/ORD/NHEERL  
(conference call)OTHER ATTENDEES: Kelly Schumacher (HED/RAB2), Karlyn Bailey (HED/RAB2),  
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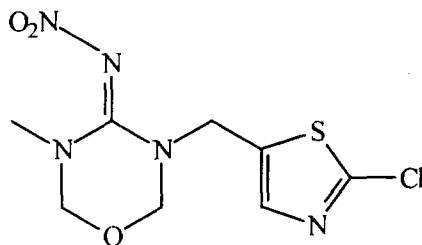
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## I. INTRODUCTION

On April 27, 2005 the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of Thiamethoxam.

## II. BACKGROUND INFORMATION

Thiamethoxam, **PC Code 060109** (4H-1,3,5-oxadiazin-4-imine, 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-; CAS No. 153719-23-4) is a broad spectrum insecticide belonging to the class of compounds call neonicotinoids. The molecular weight is 291.7 and the molecular formula is  $C_8H_{10}ClN_5O_3S$ . Thiamethoxam is currently registered for food uses. The chemical structure is as follows:



In a chronic toxicity/carcinogenicity study in rats, 50 rats/sex/dose received thiamethoxam at dietary levels of 0, 10, 30, 500 or 1500 ppm for males (0, 0.41, 1.29, 21, or 63 mg/kg/day, respectively) and 0, 10, 30, 1000, or 3000 ppm for females (0, 0.48, 1.56, 50.3, or 155 mg/kg/day, respectively) for 24 months (MRID 44718708). In the carcinogenicity study in mice, thiamethoxam was administered in the diet to 50 mice/sex/group at 0, 20, 500, 1250, or 2500 ppm (0, 0.65, 2.63, 63.8, 162 or 354 mg/kg/day for males and 0, 0.89, 3.68, 87.6, 215, or 479 mg/kg/day for females, respectively) for 18 months (MRID 44703326).

In 1999, Syngenta Crop Protection (then Novartis, Inc.) submitted a weight-of-evidence document that was reviewed by EPA. In June 2000, thiamethoxam was classified as "Likely to be Carcinogenic to Humans" by the EPA and a linear low-dose extrapolation approach for the quantification of human cancer risk based on the most potent liver tumor response observed in mice (US EPA, 2000). At the time, this approach was supported by the lack of confirmation of the carcinogenic mode of action for mouse liver tumors induced by thiamethoxam. EPA suggested that additional data were needed to supplement the proposed mode of action.

These data have been submitted to EPA and were reviewed by the CARC for the April 2005 meeting. They include the following:

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1. Characterization of thiamethoxam-related effects on the mouse liver at intervals over a 50-week period at 6 dose levels, including those where increased tumor incidences had been seen (MRIDs 46161513, 46161518, 46161521).
2. A 50-week study in rats at dietary concentrations of 0, 1000 and 3000 ppm thiamethoxam (MRID 46161514).
3. A comparative investigation of the hepatotoxicity of thiamethoxam and a number of its metabolites in two strains of mice in studies of up to 20 weeks duration (MRID 46161513).
4. A recovery study in mice (MRID 46161508)
5. A comparison of the hepatotoxicity of thiamethoxam in young (weanling) and adult mice (MRID 46161509).
6. Kinetics and metabolism studies following low and high single oral doses in mice (MRIDs 46161502, 46161504, 46161505, 46161512).
7. A comparative study in mice and rats of the kinetics of thiamethoxam and its metabolites following a single high oral dose and following dietary administration for up to 50 weeks (MRIDs 46161503, 46161506, 46161507).
8. Comparisons of the *in vitro* metabolism in rat, mouse and human liver (MRID 46161506).

A summary of the registrant's position was submitted and is entitled "Weight of Evidence for a Mode of Action for Thiamethoxam - Related mouse liver tumors (MRID 46161501). In this document the registrant presented the weight of evidence from these studies that supports a plausible mode of action explanation for the increased incidence of hepatic tumors in mice in a long-term thiamethoxam dietary feeding study.

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### III. MODE OF ACTION

The CARC followed the EPA's final guidelines for Carcinogen Risk Assessment (March 29, 2005) and the ILSI-RSI publication "A Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action" (ILSI, 2003) for the evaluation of carcinogenic response in animal studies and in determination of the relevance to humans. The Hill criteria (Hill, 1965) for causation were used as a general guide.

**1. Did the registrant provide sufficient evidence to establish a plausible mode of action for liver tumors in the mouse?** Yes, the CARC concluded that the available data are sufficient to support a plausible non-linear mode of action for liver carcinogenicity of thiamethoxam in mice. The CARC agrees with the registrant that, "A series of key events has been identified that form the basis for the mode of action for the development of liver tumors in mice. These include perturbation of cholesterol biosynthesis, hepatotoxicity, cell death (both as single cell necrosis and apoptosis) and a sustained increase in cell replication rates. In addition, these changes occur in a dose-dependent manner and are only seen at dose levels where tumor incidences are increased."

#### A. Key Events

Increased liver tumors (combined adenomas and carcinomas) were observed in long-term carcinogenicity studies in male and female mice at dietary concentrations of 500, 1250, and 2500 ppm of thiamethoxam. A series of time- and dose-related key events that form the basis for the mode of action for the formation of mouse liver tumors were identified at dose levels where tumor incidences were increased. Progressive steps in the mode of action include the following:

1. *Bioactivation of thiamethoxam* to a reactive key metabolite CGA330050, which induced the same changes in mouse liver as thiamethoxam itself (MRID 46161501)
2. *General perturbation of hepatocyte metabolism.* Early stage general perturbation of hepatocyte metabolism was caused by metabolite CGA330050 and included lowering of plasma cholesterol (within one week of dosing), induction of cytochrome P-450 isoenzymes, decreased protein synthesis, glycogen, and lipid accumulation (MRID 46161513, MRID 46161508). The earliest and most significant event in the process was the marked reduction in plasma cholesterol levels that occurred at  $\geq 500$  ppm (a dose level where tumor incidences were also increased) over 1-10 weeks of exposure (MRID 46161508).
3. *Hepatotoxicity and apoptosis (necrosis).* At this stage (8-50 weeks), signs of hepatotoxicity are seen (hepatocellular hypertrophy, lymphocytic infiltration and pigmentation of hepatocytes and Kupffer cells, clinical chemistry changes, single

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hepatocyte necrosis, and apoptosis). The incidence and severity of hepatocellular hypertrophy was increased at 30-50 weeks in mice treated with 2500 ppm thiamethoxam and at all time points in mice treated with 5000 ppm (MRID 46161521). There was a statistically significant 3-10 fold increase in the number of apoptotic bodies in the centrilobular region of the liver in male mice treated with  $\geq 500$  ppm for 59 days or longer (MRID 46161520). Necrosis was increased in a dose-related manner in mice treated with 500 ppm at week 40, at weeks 20, 40, and 50 in mice treated with 1250 ppm and at all time points in mice treated with 2500 or 5000 ppm (MRID 46161521). Overall, the data show that thiamethoxam treatment induces clear time- and dose-dependent histopathological changes of hypertrophy and induction of apoptosis as well as hepatocellular necrosis.

**4. Sustained Increased Cell Proliferation:** Sustained increases in cell proliferation (240%), measured specifically in centrilobular hepatocytes (the region of the liver in which single cell necrosis and apoptosis were concentrated), were observed in male mice at 500 ppm at 40 weeks (MRID 46161518). (In this study, no earlier measurements were made.)

#### *Events leading to Hepatic Neoplasia*

Studies where mice were fed diets of 0-5000 ppm thiamethoxam for 1-50 weeks: MRIDs 44703407, 44703406, 46161508, 46161509, 46161521, 46161513.

Study Weeks	Observation
1-10	<b>Liver Dysfunction:</b> decreased protein synthesis, glycogen and lipid accumulation, reduced cholesterol, cytochrome P-450 induction and hepatocellular hypertrophy
10-50	<b>Hepatotoxicity:</b> increased ALAT/ASAT, pigmentation, inflammatory cell infiltration, hepatocellular hypertrophy, single cell necrosis and increased apoptosis
20-50	<b>Sustained increase in cell replication rates</b>
50-80	<b>Neoplasia</b>

#### **B. Reversibility of Effects**

Preneoplastic changes induced by thiamethoxam are considered to be reversible. Continued administration of thiamethoxam is necessary to progress to stages beyond hepatotoxicity (including cell death, increases in cell replication and permanent cell transformation to neoplasia). Mice were fed 2500 ppm of thiamethoxam for 4 weeks and then given control diet for 4 weeks (MRID 46161508). After 4 weeks of treatment, plasma cholesterol was reduced to

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63% of control value, liver weights were increased by 9%, and there was a reduction of eosinophilia of centrilobular hepatocytes. After 2 weeks on the control diet, plasma cholesterol levels had returned to control values and liver histology was normal. Liver weights were normal within 4 weeks.

### **C. Mouse Strains**

Hepatic tumors and events described above were observed in the Tif:MAG mouse. Long-term studies with thiamethoxam metabolite CGA322704 (tested as clothianidin; Federal Register, 2003) are believed to have used the CD-1 mouse. Therefore, males of both strains were given diets of 0 or 2500 ppm thiamethoxam for 1, 10 or 20 weeks. Parameters examined were the same as those in the 50-week studies: liver biochemistry, histopathology, apoptosis (TUNEL) and cell replication rates (MRID 46161513).

At all time points, plasma cholesterol levels decreased. At 10 and 20 weeks, aminotransferase activities were increased and histopathological changes noted at these time points in the 50-week study were observed. An increase in cell replication rates was seen at 20 weeks. The magnitude of the changes observed in this study was comparable to those seen in the 50-week study. All changes were seen in both strains and to a similar degree.

### **D. Metabolites**

The ability of the major metabolites of thiamethoxam (CGAA322704, CGA330050, and CGA265307) to induce characteristic hepatic lesions observed with thiamethoxam was investigated in feeding studies in mice up to 20 weeks duration (MRID 46161510, 46161513).

CGA322704 is reported not to induce cancer in mice (or rats). In the 20-week study at 2000 ppm in the diet (same as highest dose in a chronic feeding study), the metabolite did not reduce plasma cholesterol, cause hepatotoxicity nor increase cell replication rates. Thiamethoxam (2500 ppm) in the same study was hepatotoxic and increased cell replication rates.

CGA330050 (500 and 1000 ppm; dose levels selected to mimic systemic exposure to this metabolite following high-dose levels of thiamethoxam) induced the same liver changes as those seen after thiamethoxam administration (reduced plasma cholesterol levels as well as histological changes: increased hypertrophy, single cell necrosis, apoptosis and cell replication at 10 weeks).

CGA265307 (500 ppm; a dose selected to mimic systemic exposure to this metabolite following a feeding level of 2500 ppm thiamethoxam) did not induce any hepatic lesions seen in thiamethoxam treated mice.

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**E. CGA265307 and Inhibition of Nitric Oxide (NO) Synthase**

This metabolite is structurally similar to a number of known NO synthase inhibitors. NO produced by these enzymes is known to have a regulatory role in the liver in modulating the adverse effects of  $TNF_{\alpha}$  released from endothelial cells during chemically induced hepatotoxicity. Therefore, inhibition of these enzymes could exacerbate the cytotoxicity, necrosis and apoptosis that are believed to lead to cell replication and tumors in the livers of mice fed thiamethoxam (MRID 46161511). The CARC considered this to be an ancillary event, not part of the key events.

**F. Lack of Effects on Rat Liver**

No thiamethoxam-related increases in liver tumors were reported in the 2-year rat study (males - high dose of 1500 ppm due to kidney toxicity; females - high dose of 3000 ppm as the MTD). The 50-week mouse study was repeated in female Tif:Ralf rats at doses of 0, 1000 or 3000 ppm for 1, 10, 20, 30, 40 or 50 weeks (15 rats/group). Livers were examined microscopically for morphological changes, replicative DNA synthesis was assessed by nuclear incorporation of BrdU as a diagnostic parameter for cell proliferation and the apoptotic activity was assessed by TUNEL-histochemistry. Clinical chemistry parameters were measured at each time point. Metabolic enzyme activities were measured after 1 and 10 weeks (MRID 46161519).

None of the changes seen in the mouse 50-week study were seen in the rat study. **The key events leading to hepatocarcinogenesis are only seen in the mouse.**

**G. The Role of Metabolism in Species Specificity**

Time related metabolic profiles in plasma of mice and rats is listed below (MRID 46161501).

Test Article	Mice (2500 ppm)			Rats (3000 ppm)		
	Week 1	Week 10	Week 50	Week 1	Week 10	Week 50
Thiamethoxam	12	15	10	7	19	8
CGA322704	3	5	3	1	1	1
CGA265307	2	7	4	<1	<1	<1
CGA330050	1	2	1	<1	<1	<1

UNITS =  $\mu\text{g/mL}$  plasma; This table was made from Figure 6, p. 22 of MRID 46161501.

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**H. Cross-Species Comparison of Thiamethoxam Metabolic Conversion Rates**

Metabolic pathway	Relative rate
	<b>mouse : rat</b>
Thiamethoxam to CGA265307 via CGA322704	54 : 1
Thiamethoxam to CGA265307 via CGA330050	87 : 1
	<b>mouse : human</b>
Thiamethoxam to CGA265307 via CGA322704	371 : 1
Thiamethoxam to CGA265307 via CGA330050	238 : 1

The above table indicates that the conversion of thiamethoxam to the metabolite CGA265307 via either pathway (CGA322704 or CGA330050) is greater in the mouse than in either the rat or human.

**I. Summary of Mode of Action**

The CARC agrees with the Registrant's summary of the mode of action as follows: "A number of key events have been identified which are believed to lead to liver cancer in mice fed diets containing thiamethoxam. These include a reduction in plasma cholesterol, cytotoxicity in the form of single cell necrosis and apoptosis, and an increase in cell replication rates. The changes occur in a dose-dependent manner and are seen only at the dose levels where cancer incidences were increased. They form a rational temporal sequence with biochemical changes leading to cell death followed by increased cell replication. These events are also highly dependent on the duration of dosing; cholesterol changes are seen within one week, cytotoxicity after 10 weeks of dosing and cell replication increases after 20 weeks. The changes are reproducible between studies and between strains of mice and the early changes are rapidly reversible when the test diets are removed."

"None of these changes were seen in rats fed on diets containing thiamethoxam, nor were they seen in mice fed a diet containing CGA322704, a non-carcinogen. The key metabolite responsible for the hepatic changes in mice has been identified as CGA330050, a metabolite that is formed from thiamethoxam but not CGA322704. These hepatic changes are exacerbated by another important metabolite, CGA265307."

"The correlation between key events and liver tumors is absolute within these studies. It is consistent with the species differences in carcinogenicity and internally consistent with the known metabolism of thiamethoxam."

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## 2. Is the Animal Mode of Action Plausible in Humans?

### A. Key Events Across Species

**Sufficient evidence for a mode of action in the mouse has been established.** To be relevant to humans, the key events that were identified in the test species should be concordant in humans. The concordance table below represents this concept and analysis, where each key event is matched across species and directly to humans.

Key Event	Mouse	Rat	Human
Generation of critical metabolites: CGA330050 and CGA265307	Yes	Yes	Yes (1)
CGA330050-related liver “dysfunctional” changes: ↓ cholesterol biosynthesis; ↓ protein synthesis; ↑ P-450	Yes chol=500 ppm <sup>a</sup> protein=2500 ppm	No; (insufficient CGA 330050)	Unlikely (1) (insufficient CGA 330050)
CGA265307 inhibition of inducible nitric oxide synthase (iNOS). <b>The CARC considered this to be an ancillary event.</b>	Yes 2500	No; (insufficient CGA 265307)	Unlikely; (insufficient CGA 265307)
Hepatotoxicity (clinical chemistry; histopathology; apoptosis)	Yes cl chem=2500 ppm histo=2500 ppm apop≥500 ppm necrosis≥500 ppm	No	<i>In vivo</i> data not available
Sustained increase in cell replication	Yes ≥500 ppm	No	<i>In vivo</i> data not available
Tumors	Yes 500 ppm ~ 113% 1250 ppm ~ 130% 5000 ppm ~ 165%	No	Unlikely

(1) = based on *in vitro* data

a = dose at which effect occurred

The CARC concluded that while the mode of action is plausible in humans, it is dependent on a sufficient amount of the active metabolite being persistently formed to drive the toxicity and regenerative proliferation. The table shows that the progression of key events in rats and humans does not go beyond the generation of CGA330050 and CGA265307. The CARC concluded that the *in vitro* data showed that the metabolic capability of humans is more similar to rats than mice; however, the *in vitro* human data are too limited to draw quantitative kinetic conclusions.

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**B. Are Young Animals more Sensitive than Adults?**

## Comments:

1. histopathological changes in the liver not seen until 10 weeks
2. mice reach maturity at 6-7 weeks
3. earliest key event: one week, reduction of plasma cholesterol

## Study:

Groups of 6 male weanling mice (21 days old) and groups of 6 male adult mice (15-17 weeks old) were fed diets of 0, 500, 1250 and 2500 ppm thiamethoxam for 7 days (MRID 46161509). Plasma cholesterol was measured at the end of the study. Dietary intake was higher in weanlings than adults (about 2x based on concentration of the major metabolites at the end of the study). Plasma cholesterol levels were lowered in adults at all 3 levels, but only at 1250 and 2500 ppm in weanlings. The magnitude of the response in weanlings at the two higher doses was also less than in adults.

## Conclusion:

Infants and children would not be more susceptible than adults.

**3. Conclusions**

The CARC agreed with the registrant that a plausible mode of action has been established for the development of liver tumors in a mouse bioassay with thiamethoxam. It is concluded that the liver tumors in the mouse arise through a non-genotoxic mode of action characterized by a series of key events that include: perturbation of cholesterol biosynthesis, hepatotoxicity, cell death (both as single cell necrosis and apoptosis) and a sustained increase in cell replication rates. Neither the key events nor an increase in liver tumors are seen in rats fed on diets containing up to 3000 ppm thiamethoxam. The key metabolites, CGA330050 and CGA265307, responsible for the key events in the mouse are not formed in sufficient quantities in the rat and explain the lack of a carcinogenic response in this species.

A sufficient amount of active metabolite must be produced along with persistent exposure to the active metabolite to lead to the hepatotoxic/regenerative proliferative/neoplastic response in the mouse. Limited human *in vitro* metabolism studies suggest that humans are more similar to the rat compared to the mouse in producing the active metabolite. The rat does not develop tumors following treatment with thiamethoxam. Thus, the mouse appears to be uniquely sensitive to this mode of action. Because of the threshold nature of the mode of action and the unique sensitivity of the mouse, it is concluded that humans are unlikely to be at risk for developing tumors

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following exposures to thiamethoxam.

#### IV. WEIGHT-OF-EVIDENCE CONSIDERATION

##### A. Hazard Identification

###### *Mouse*

Dietary administration of thiamethoxam was associated with increased incidence of liver tumors in both sexes of mice.

**In male mice**, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 5, 20, 500, 1250, 2500 ppm dose groups, respectively, were as follows:

Adenomas:	11/50 (22%), 5/50 (10%), 10/49 (20%), 17/50 (34%), 27/48 (56%), 40/50 (80%)
Carcinomas:	1/50 (2%), 4/48 (8%), 2/46 (4%), 5/50 (10%), 7/46 (15%), 20/49 (41%)
Combined:	12/50 (24%), 7/50 (14%), 12/49 (24%), 19/50 (38%), 27/48 (56%), 45/50 (90%)

Male mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for hepatocellular adenomas, carcinomas, and adenomas and/or carcinomas combined, all at  $p < 0.01$ . There were also significant differences in the pair-wise comparisons of the 1250 ppm dose group with the controls for hepatocellular adenomas and adenomas and/or carcinomas combined, both at  $p < 0.01$ , and for hepatocellular carcinomas at  $p < 0.05$ .

**In female mice**, the incidences of liver adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 5, 20, 500, 1250, 2500 ppm dose groups, respectively, were as follows:

Adenomas:	0/48 (0%), 0/50 (0%), 0/49 (0%), 5/44 (11%), 8/47 (17%), 31/49 (63%)
Carcinomas:	0/48 (0%), 0/50 (0%), 0/49 (0%), 0/44 (0%), 2/47 (4%), 11/49 (22%)
Combined:	0/48 (0%), 0/50 (0%), 0/49 (0%), 5/44 (11%), 9/47 (19%), 32/49 (65%)

Female mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for hepatocellular adenomas, carcinomas, and adenomas and/or carcinomas combined, all at  $p < 0.01$ . There were also significant differences in the pair-wise comparisons of the 500 ( $p < 0.05$ ) and 1250 ( $p < 0.01$ ) ppm dose groups with the controls for hepatocellular adenomas and adenomas and/or carcinomas combined. The incidence of carcinomas in females at 500 and 1,250 ppm, although not statistically significant, exceeded the concurrent and historical control values. The increases in these tumors in males at 500 ppm were considered to be

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biologically significant and were supported by a dose-related increase in the incidence and severity of non-neoplastic lesions.

The incidences of adenomas and carcinomas at  $\geq 500$  ppm exceeded the historical control ranges (males: 10%-46% and 0%-24%, respectively; females: 0%-8% and 0%-2%, respectively). The CARC reaffirmed the previous CARC's conclusion that the liver tumors in male and female mice were treatment-related.

Dosing at the highest dose was considered adequate and not excessive based on decreased body weight gains in both sexes and histopathological changes in the liver and kidney.

*Rat*

Thiamethoxam was not carcinogenic in male or female rats dose levels of up to 1500 ppm in males and 3000 ppm in females. The CARC revisited the adequacy of dose issue according to HED's Dose Selection Paper. They determined that dosing in male rats at 1500 ppm was adequate based on the results of the 90 day study. In the 90-day study at 1250 ppm, there was decreased body weight/body weight gain of 15%/22%, increased creatinine, and kidney pathology (chronic tubular lesions) in males rats. In female rats, dosing at 3000 ppm could have been tested higher; however, since the mode of action is known and the regulatory doses are below 3000 ppm, the CARC determined that a new rat study will not impact the risk assessment.

**B. Mutagenicity**

Thiamethoxam was negative in both *in vitro* and *in vivo* mutagenicity assays.

**C. Mode of Action**

The CARC agreed with the registrant that a plausible mode of action has been established for the development of liver tumors in a mouse bioassay with thiamethoxam. It is concluded that the liver tumors in the mouse arise through a non-genotoxic mode of action characterized by a series of key events that include: perturbation of cholesterol biosynthesis, hepatotoxicity, cell death (both as single cell necrosis and apoptosis) and a sustained increase in cell replication rates. These changes occurred in a time- and dose-dependant manner and are only seen at dose levels where tumor incidences are increased. Neither the key events nor an increase in liver tumors are seen in rats fed on diets containing up to 3000 ppm thiamethoxam. The key metabolites, CGA330050 and CGA265307, responsible for the key events in the mouse are not formed in sufficient quantities in the rat and explain the lack of a carcinogenic response in this species.

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While humans are *qualitatively* capable of generating the active hepatotoxic metabolite, limited *in vitro* human metabolism studies suggest humans appear to be more like the rat in that they are less efficient at producing the active metabolite. The mode of action is dependant on a sufficient amount of active metabolite persistently produced to drive the carcinogenic response. Humans are unlikely to be at risk of developing liver tumors as a result of exposure to thiamethoxam due to these two characteristics (the threshold response coupled with the difference in species sensitivity).

#### V. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified Thiamethoxam as "**Not Likely to be Carcinogenic to Humans**" based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse and that the carcinogenic effects are a result of a mode of action dependent on sufficient amounts of a hepatotoxic metabolite produced persistently. Although humans are qualitatively capable of producing the active metabolite, thiamethoxam is unlikely to pose a cancer risk to humans unless sufficient amounts of metabolites are persistently formed to drive a carcinogenic response. Based on limited *in vitro* human metabolism data and comparative metabolism studies in the mouse and rat, the human appears to be more like the rat, which does not develop tumors after thiamethoxam treatment. Lastly, the non-cancer assessment is sufficiently protective of the key events (perturbation of liver metabolism, hepatotoxicity/regenerative proliferation) in the animal mode of action and, thus, cancer is not an issue.

#### VI. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Not Required.

THIAMETHOXAM

CANCER ASSESSMENT DOCUMENT

FINAL

**VII. BIBLIOGRAPHY**

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